Chapter 15
Gallbladder and Biliary Disease

A1. Fully characterize at least 10 murine *Lith* genes related to cholesterol gallstones. Continuous momentum is being generated to dissect out murine genes that are causally correlated to cholesterol gallstone formation, including intestinal *Apob48* (Wang HH. *Hepatology* 2005;42:894), sterol transporters *Abcg5*, *Abcg8*, and *Npc111* (Wittenburg H. *Mamm Genome* 2005;16:495), and estrogen receptor alpha (Wang HH. *J Lipid Res* 2005; Epub) (20%)

A2. Develop small animal model for cholangiopathies that would allow analysis of effects of chronic necroinflammation on biliary epithelium. Bile duct ligation in the rat is the standard animal model for cholangiocyte injury, which has been used to assess the role of cell signaling molecules. The *Mdr2* (*Abcb4*) knock-out mouse has been shown to develop toxic bile and liver disease that resembles PSC and can used to assess novel therapeutics (Popov Y. *J Hepatol* 2005;43:1045). A recent program announcement ("Animal Models of NIDDK-Relevant Diseases," PA-05-049) encourages applications to develop animal models of cholangiopathies. (20%)

A3. Develop molecular imaging techniques for visualization of the biliary tract that would provide accurate assessment of size, shape, position, motility, and inflammation, as well as a means of early detection and staging of neoplasia. Positron emission tomography, using metabolic mapping of cellular function with fluorodeoxyglucose, may afford better imaging of cholangiocarcinoma and earlier diagnosis (Reinhardt MJ. *J Nucl Med* 2005;46:1158). Development of novel, non-invasive imaging techniques for the detection of cholangiocarcinoma is encouraged in the program announcement on "Non-Invasive Methods for Diagnosis and Progression" (PA-04-088). (10%)

B1. Develop a cohort study of calculous and acalculous biliary pain to allow for analysis of risk factors and roles of genetic factors, microlithiasis, gallbladder motility, sphincter of Oddi dysfunction, and nucleation factors. A small grant has been funded to develop a clinical network on sphincter of Oddi dysfunction, an area specifically highlighted in the program announcement "Endoscopic Clinical Research in Pancreatic and Biliary Diseases" (PAR-03-033). (10%)

B2. Characterize the role of enterohepatic species of *Helicobacter* and other candidate bacteria in development of cholesterol gallstones in both mice and humans. Different *Helicobacter* species but not *Helicobacter pylori* have different abilities to induce gallstones in mice fed lithogenic diets (Maurer KJ. *Amer J Physiol* 2005;290:G175). Using molecular techniques, DNA sequences of *Helicobacter* species have been found in cholecystic bile in humans (Neri V. *Aliment Pharmacol Ther* 2005; 22:715). (10%)

B3. Identify plasma or urine markers for lithogenicity of bile using proteomics or metabolomics. Grant applications using proteomics and metabolomics to characterize liver and biliary diseases have been encouraged in program

announcements, including PA-04-081 ("Proteomics: Diabetes, Obesity, and Endocrine, Digestive, Kidney, Urologic, and Hematologic Diseases"). (0%)

C1. Establish prospective database on cohort of patients with high risk of gallbladder cancer (e.g., American Indians) to allow development and assessment of means of early diagnosis and management. Epidemiological analysis on the risk factors of gallbladder cancer have confirmed a higher incidence (4.1 times in males; 2.6 times in females) of gallbladder cancer amongst American Indians and Alaska natives when compared with age- and sex-matched white populations (Paltoo DN. *Public Health Rep* 2004;119:443). No prospective studies have been initiated. (0%)

C2a. Identify at least 5 human *LITH* genes associated with increased risk of gallstones, based upon homology with murine genes and family studies. Using intercrosses between mouse strains, several new loci for cholesterol gallstone formation have been identified and one (*Lith9*) has been linked to the cholesterol transporter genes *Abcg5/Abcg8*, which have human homologues that are believed to be important in cholesterol gallstone formation (Wittenburg H. *Mamm Genome* 2005;16:495). (10%)

C2b. Develop noninvasive biomarker for cholangiocarcinoma. Prospective studies on primary sclerosing cholangitis have included collection of serial serum samples in patients who are at high risk for developing cholangiocarcinoma. Research grants on development of biomarkers have been encouraged by program announcements (PA-05-098: "Development of Disease Biomarkers"). (0%)

C3. Develop practical and effective approach to or means of prevention of cholesterol gallstones in high-risk populations. Until the etiology and specific risk factors for development of gallstones has been fully elucidated, practical and effective approaches to prevention will not be possible. In a long-term study in a large cohort of women, high-carbohydrate, high-glycemic response diets were associated with higher subsequent risks of cholecystectomy (Tsai CJ. *Gastroenterology* 2005;129:105). (10%)

Figure 17. Estimated Progress on Gallbladder and Biliary Disease Research Goals, 2005 (Year 1)